REVIEW

Randomized Trials for Endovascular Treatment of Infrainguinal Arterial Disease: Systematic Review and Meta-analysis (Part 1: Above the Knee)

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WHAT THIS PAPER ADDS

In patients with intermittent claudication, endovascular treatment of above-the-knee arterial lesions should preferably be performed using balloon angioplasty. When balloon angioplasty does not result in less than 30% residual stenosis, or a flow limiting dissection occurs, bailout stenting may be performed. Scientific evidence for using drug-eluting stents is inconclusive, and, as it is unknown if they perform better, it is recommended to use the less expensive bare stents. For patients with critical limb ischemia and only above-the-knee lesions, no substantial evidence is available to recommend a specific endovascular treatment strategy.

Objective: To evaluate 1 to 36 month follow-up outcomes of different endovascular treatment strategies in above-the-knee (ATK) arterial segments in patients with intermittent claudication (IC) and critical limb ischemia (CLI).

Methods: Studies indexed in Medline and Embase from 1980 to November 2013 of randomized controlled trials comparing balloon angioplasty (PTA) or drug-eluting balloon (DEB) with optional bailout stenting, or primary stenting using a bare stent (BS) or drug-eluting stent (DES) to one another were included. Methodological quality of each trial was assessed using the Cochrane Collaboration tool, and quality of evidence was assessed using the GRADE system. Outcomes assessed were quality of life, walking capacity evaluated by treadmill or questionnaire, change in Rutherford classification, target lesion revascularization (TLR), bypass, binary restenosis, late lumen loss, stenosis grade, amputation, death, major adverse cardiac events, or event-free survival with follow-up periods of at least 1 month.

Results: Twenty-three trials including 3314 patients in total were identified. Eighty-five per cent patients had IC and 15% CLI. Fifteen trials showed no systematic benefit of BS over PTA. One trial comparing DES and PTA reported no significant differences in walking capacity or Rutherford classification. Four trials showed a beneficial effect on TLR rate, but not on Rutherford classification of DEB compared with PTA. In four trials DES did not systematically perform better than BS.

Conclusion: In general, performing PTA with optional bailout stenting for ATK lesions is the preferred strategy in patients with IC. For CLI, more studies are needed for recommending an optimal treatment strategy.

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INTRODUCTION

Single or multiple chronic stenoses or occlusions in the lower limb arteries can result in intermittent claudication (IC) or critical limb ischemia (CLI). Patients with IC have limited walking capacity because of muscle discomfort, which reduces their quality of life.[1] Patients with CLI present with ischemic rest pain or ischemic tissue loss with limited or even absent healing. If not treated adequately or when treatment is unsuccessful, amputation in these patients may be inevitable.[1]

The aims of treatment for IC or CLI are very different. For patients with IC, the goal is to restore walking capacity, and improve quality of life. For CLI, the objective is to prevent amputation by establishing wound healing, and to relieve ischemic rest pain. To achieve this, immediate restoration of blood flow is essential. Revascularization can be performed surgically or endovascularly, but endovascular treatment is preferred because it is less invasive than open surgery.[1] For IC, invasive treatment is only indicated when supervised

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exercise or medical therapy fails to relieve symptoms, and the decline in walking capacity is invalidating.[1]

For patients with above the knee (ATK) lesions the TransAtlantic Inter-Society Consensus II (TASC II)[1] currently recommends performing balloon angioplasty (PTA) with optional bailout stenting. However, over the past decade several other endovascular revascularization strategies have been proposed, such as drug-eluting balloon (DEB) angioplasty with optional bailout stenting, or primary stenting using a bare stent (BS) or drug-eluting stent (DES). It is as yet unclear if these innovations result in better treatment outcomes that are clinically relevant.

The aim of our study was to determine the optimal treatment strategy for patients with IC or CLI caused by ATK arterial lesions. As randomized controlled trials (RCTs) provide the best evidence on the relative effectiveness of revascularization strategies by a direct comparison of clinically relevant outcomes, we performed a systematic review of the 1 to 36 month follow-up outcomes of RCTs comparing different endovascular treatment strategies in ATK arterial segments in patients with CLI and IC.

MATERIALS AND METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[2] The protocol of this review was not published or registered in advance.

Eligibility criteria

Types of studies. RCTs.
Types of patients. Patients with IC or CLI treated for ATK arterial stenosis or occlusion.
Types of intervention. Studies comparing (1) BS versus PTA, (2) DES versus PTA, (3) DEB versus PTA, and (4) DES versus BS.
Types of outcome measures. Quality of life, walking capacity evaluated by treadmill or questionnaire, change in Rutherford classification, TLR, bypasses performed, binary restenosis (or patency), late lumen loss, stenosis grade, amputation, death, major adverse cardiac events (MACE), and event-free survival (EFS) for follow-up periods of at least 1 month. EFS is defined as free from death, target vessel revascularization, major or minor amputation, or myocardial infarction.

Outcomes for the PTA strategy were only eligible when bailout stenting was not considered as a failure in data analysis.

Information sources

Electronic databases, Medline (PubMed) and OVID Embase, were searched from 1980 to the present. The last search was performed on 5 November 2013. The literature search was performed with the help of a clinical librarian. No limits were applied.

Search strategy

The search strategy for both Medline and Embase consisted of three components: peripheral arterial disease, angioplasty/stent, and RCT. For these components several search terms were formulated. These terms were combined using 'OR', and the three components were combined using 'AND'. Completeness of the search was checked by verifying whether previously assessed relevant articles were found. If articles were missed, relevant search terms were added to the search strategy.

A detailed search strategy is provided in Appendix 1 (online supplementary material).

Study selection

Two authors (SJ and AC) independently assessed eligibility by screening the titles and abstracts of the identified articles according to the eligibility criteria. After this initial selection, both authors independently assessed the full texts of the potential relevant articles for eligibility. After selection, discrepancies between the authors were resolved by discussion and consensus was reached.

Methodological quality and risk of bias in individual studies

For assessing methodological quality the Cochrane Collaboration's tool for assessing risk of bias was used.[3] This tool has been specifically developed for assessing the risk of bias in RCTs on seven items: selection bias considering (1) adequateness of random sequence generation and (2) allocation concealment, (3) performance bias considering adequateness of blinding participants and personnel during intervention, (4) detection bias considering adequateness of blinding during outcome assessment, (5) attrition bias considering completeness of outcome data, (6) reporting bias considering adequateness of reporting outcomes, and (7) other biases. All items were scored as adequate, unclear, or inadequate, as defined by the Cochrane Collaboration. Additionally, the presence of baseline differences between the intervention and the comparator strategies for several risk factors (i.e. age, gender, smoking, diabetes mellitus, renal failure, coronary artery disease, hyperlipidemia, hypertension, Fontaine or Rutherford stage, lesion calcification, stenosis grade, number of occlusions, and lesion length) were scored. Items were scored as 'adequate' when all relevant risk factors were reported, and all did not differ significantly between strategies; 'inadequate' when one or more of the relevant risk factors differed significantly between strategies; or 'unclear' when risk factors reported did not differed significantly, but not all relevant risk factors were reported. When there were multiple publications on the same RCT, the methodological quality was assessed only once.

Data extraction

Data extraction was performed in a standardized manner using a data extraction form. Two authors (SJ and AC) independently extracted the data from the included articles.

Consensus was reached after independent data extraction. Disagreements were resolved by discussion.

The following data were extracted: study design, that is intervention and comparator characteristics, pre- and post-interventional antiplatelet therapy; study population characteristics, for example age, gender, and several risk factors such as presence of diabetes mellitus and smoking status; and outcomes reported, as defined by the eligibility criteria. For the outcomes quality of life, walking capacity evaluated by treadmill or questionnaire, death, MACE, and EFS data were extracted on a per-patient basis. Data on change in Rutherford classification, TLR, bypasses performed, binary restenosis, late lumen loss, stenosis grade, and amputation preferably were extracted on a per-limb/per-lesion basis.

For dichotomous data, extraction of data presented by survival analysis, that is hazard ratio (HR, calculated using Cox-regression analysis) with standard error (SE) or event rate per strategy, and the *p* value (calculated by Cox-regression analysis or the Log Rank test), were preferred. If not reported, raw data of the number of events versus no events were extracted.

For continuous data the mean or median scores with standard deviation (SD) or range and total number of patients were extracted when possible. If not reported, the mean difference with SE and *p* value (either calculated by an independent *t* test, Mann–Whitney test, or by ANCOVA) were extracted. For outcomes with three or more categories, that is data from Rutherford change, data per category and *p* value (calculated by χ^2 test) were extracted. Authors were not contacted in case of missing data.

Summary estimates of outcomes

Overview of summary estimates. Multiple outcomes were of interest for this review. The summary measure, therefore, depended on the outcome assessed. For dichotomous outcomes such as change in Rutherford classification (when dichotomized), TLR, bypasses performed, binary restenosis (or patency), amputation, death, and MACE, the risk ratio (RR) was the principle summary measure. For continuous outcomes such as quality of life, walking capacity evaluated by treadmill or questionnaire, late lumen loss, and stenosis grade, the summary measure was the weighted mean difference (MD) between strategies.

Pooling of summary estimates. Data were pooled using the random effects model. Heterogeneity was not tested statistically, but assumed a priori, because of differences in population and lesion characteristics and the use of different types of stents or balloons between studies.

Data were only pooled for the comparisons of BS versus PTA, DES versus PTA, DEB versus PTA, and DES versus BS when follow-up duration was similar between studies. For pooling of dichotomous data the RR were calculated, and for continuous data the weighted MD, with 95% confidence interval (95% CI) and *p* value. Data reported as median and range were not converted to mean and SD, respectively, and were therefore excluded from meta-analysis. Summary estimates were calculated with Review Manager (RevMan, Version 5.2. The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2008). For dichotomous data that had no *p* value readily available, the *p* value was calculated using the Fisher's exact test in GraphPad Prism (Version 5.01, GraphPad Software, La Jolla, CA, USA, www.graphpad.com). If $p < .05$, the RR with 95%CI was calculated using Review Manager.

Quality of evidence

For every outcome, the quality of evidence was assessed in consensus by two authors (SJ and AC) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[4] This system divides the quality of results into four categories: high (++++), moderate (+++), low (++), and very low (+) quality. To assess the quality for RCTs, the quality initially was graded as high (++++), but downgraded if risk of bias, inconsistency of results, indirectness of evidence, imprecision, or publication bias is present. For this review, because of the inability to assess inconsistency and publication bias for most outcomes, quality of evidence was downgraded to moderate quality (+++) in advance for all outcomes. Indirectness of evidence was graded as absent in advance, as the eligibility criteria included only studies that evaluated patients with IC or CLI. Therefore, quality of evidence was only downgraded to low quality (++) when risk of bias or imprecision was present, or to very low quality (+) when risk of bias and imprecision were present. Risk of bias was defined as present, when five or more items on the Cochrane Collaboration's tool were graded as unclear or high risk of bias. Imprecision was defined as present when less than 100 patients were evaluated for an outcome. When meta-analysis of an outcome could be performed, quality of evidence was downgraded when the average risk of bias of the relevant RCTs had five or more items with a high risk of bias. When the pooled data had outcomes on less than 100 patients, quality of evidence was downgraded.

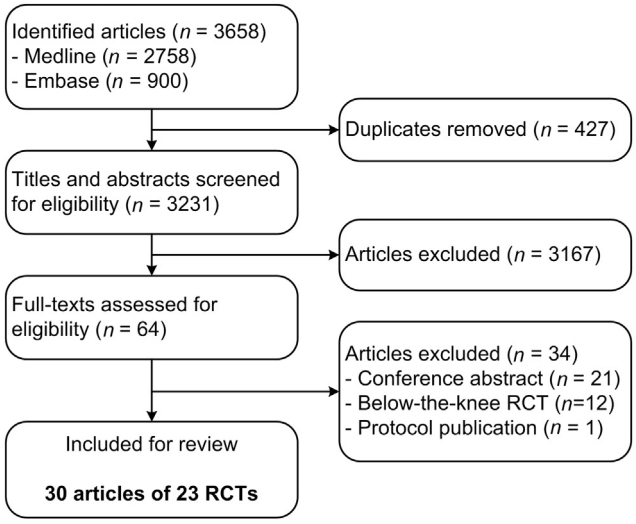

Figure 1. Flow diagram of search and study selection. RCT, randomized controlled trial.

Table 1. Study and patient characteristics.

Study	Comparison	Patients, *N*	% FII/ FIII/ FIV or IC/CLI	Lesions, *N*	Age (y), mean (SD) or median (range)	Males, *N* (%)	Smoking, *N* (%)	Diabetes, *N* (%)	Renal failure, *N* (%)	CAD, *N* (%)	Stroke, *N* (%)	Hyperlip., *N* (%)	Hypertens., *N* (%)	Occlusions, *N* (%)	Stenosis, % (mean/ SD)	Lesion length (mm), mean (SD)	Primary outcome	Industry sponsored
BS vs PTA																		
Brancaccio 2012[5]	Nitinol-S	50	42/24/ 34	50	73 (—)	23 (46)	20 (40)	20 (40)	7 (14)	7 (14)	—	31 (62)	34 (68)	—	—	—	Embolic load	No
Laird 2010/ 2012[6,7]	Nitinol-S	206	100/0/0	234	67 (10)	143 (69)	156 (76)	79 (38)	—	114 (55)	—	162 (79)	180 (87)	41 (18)	74 (18)	68 (43)	1 y TLR	Yes
Dick 2009[8]	Nitinol-S	73	95/1/4	73	69 (10)	50 (68)	29 (40)	22 (30)	—	24 (33)	4 (5)	67 (92)	60 (82)	28 (38)	90 (16)	73 (57)	6 mo restenosis	No
Saxon 2003/ 2008[9,10]	PTFE-Nitinol-S	197	FII—FIV	197	67 (10)	150 (76)	96 (49)	70 (36)	16 (8)	94 (48)	17 (9)	117 (59)	133 (68)	49 (25)	70 (40)	70 (40)	1 y primary patency with ABI change <.15	Yes
Sabeti 2007[13]/ Schillinger 2007[11]/ Schillinger 2006[12]	Nitinol-S	104	87/3/10	104	67 (10)	55 (53)	46 (44)	39 (38)	—	74 (71)	7 (7)	93 (89)	95 (91)	36 (35)	90 (10)	96 (70)	6 mo binary restenosis	No
Krankenberg 2007[14]	Nitinol-S	244	FI—FIV (2 pts FI)	244	66 (10)	168 (69)	172 (70)	81 (33)	25 (10)	90 (37)	20 (8)	148 (61)	202 (83)	75 (31)	86 (7)	45 (28)	1 y binary restenosis	Yes
Greenberg 2004[15]	Nitinol-S	266	FII—FIV	352	68 (10)	170/ 260 (65)	208/257 (81)	98/260 (38)	—	85/256 (34)	—	—	—	—	—	34 (30)	30 day death, periprocedural MI and 9 mo TLR	No
Chalmers 2013[16]	Nitinol-S	150	82/18	150	68 (9)	123 (82)	38 (25)	52 (35)	17 (11)	58 (39)	—	—	100 (67)	140 (93)	—	120 (53)	1 y binary restenosis	Yes
Rastan 2013[17]	Nitinol-S	246	79/21	246	Mean 73 (41—89)	158 (64)	57 (23)	91 (37)	—	106 (43)	—	194 (79)	210 (85)	81 (33)	—	42 (30)	1 y primary patency	Yes
Grenacher 2004[18]	Palmaz-S	116 pts (124 limbs)	76/8/16	124	67 (10)	80 (65)[a]	59 (48)[a]	54 (44)[a]	—	—	—	67 (54)[a]	61 (49)[a]	39 (31)	84 (14)	15 (12)	1 and 2 y primary patency	Not reported
Grimm 2001[19]	Palmaz-S	53	100/0/0	53	69 (9)	—	—	—	—	—	—	—	—	16 (30)	88 (13)	29 (20)	Unclear	Not reported
Cejna 1999/ 2001[20,21]	Palmaz-S	141 pts (154 limbs)	70/12/ 18	186	Mean 67 (39—87)	95 (62)[a]	92 (60)[a]	63 (41)[a]	—	—	—	69 (45)[a]	67 (44)[a]	60 (39)	—	24 (2)	12 mo primary patency	Not reported
Zdanowski 1999[22]	Stent	32	15.5/ 19/ 65.5	32	Median 71 (41—86)	14 (44)	11 (34)	10 (31)	—	—	—	—	8 (25)	32 (100)	100 (0)	72 (20 —200)	Unclear	Not reported
Vroegindeweij 1997[23]	Palmaz-S	51	100/0/0	51	Mean 64 (41—82)	36 (71)	32 (63)	6 (12)	—	15 (29)	—	16 (31)	9 (18)	9 (18)	—	—	Unclear	Not reported

Continued

Table 1-*continued*

Study	Comparison	Patients, *N*	% FII/ FIII/ FIV or IC/CLI	Lesions, *N*	Age (y), mean (SD) or median (range)	Males, *N* (%)	Smoking, *N* (%)	Diabetes, *N* (%)	Renal failure, *N* (%)	CAD, *N* (%)	Stroke, *N* (%)	Hyperlip., *N* (%)	Hypertens., *N* (%)	Occlusions, *N* (%)	Stenosis, % (mean/ SD)	Lesion length (mm), mean (SD)	Primary outcome	Industry sponsored
Becquemin 2003[24]	Palmaz-S	227	79/6/15	227	66 (11)	142 (63)	148 (65)	27 (12)	—	59 (26)	16 (7)	91 (40)	118 (52)	50 (22)	—	25 (18)	1 y binary restenosis	Yes
DES vs PTA																		
Dake 2011/ 2013[25,26]	PTX-ES	474	91.5/5/ 3.5	498	68 (10)	307 (65)	404 (85)	216 (46)	49 (10)	91 (19)	—	346 (73)	404 (85)	135 (27)	79 (17)	54 (40)	1 y EFS	Yes
DEB vs PTA																		
Werk 2008[27]	PTX-EB	87	94/6/0	87	69 (—)	52 (60)	36 (41)	41 (47)	—	—	—	50 (57)	69 (79)	14 (16)	84 (14)	59 (8 —226)	6 mo LLL	Yes
Tepe 2008[28]	PTX-EB	102	FII—FIV	102	68 (9)	65 (64)	23 (23)	49 (48)	—	—	—	67 (66)	83 (81)	27 (26)	90 (7)	74 (65)	6 mo LLL	Yes
Werk 2012[29]	PTX-EB	91	96/2/2	107	71 (8)	56 (62)	49 (54)	32 (35)	—	29 (32)	7 (8)	44 (48)	60 (66)	28 (31) in patients	77 (—)	68 (54)	6 mo LLL	Yes
Fanelli 2012[30]	PTX-EB	—	FII—FIV	92	—	—	—	—	—	—	—	—	—	14 (15)	84 (4)	—	6 mo LLL	No
DES vs BS																		
Lammer 2013[31]	Heparin-ES vs nitinol-S	141	FII—FIV	141	69 (9)	100 (71)	98 (70)	50 (35)	17 (12)	31 (22)	—	96 (68)	118 (84)	102 (72)	—	182 (65)	1 y primary patency	Yes
Duda (SIROCCO I) 2002/2006[32,34]	Sirol-ES vs nitinol-S	36	FII—FIII	36	66 (—)	27 (75)	9 (25)	—	—	13 (36)	—	21 (58)	25 (69)	21 (58)	88 (17)	86 (—)	6 mo stenosis	Yes
Duda (SIROCCO II) 2005/2006[33,34]	Sirol-ES vs nitinol-S	57	FII—FIII	57	67 (10)	4 (70)	26 (46)	22 (39)	—	28 (49)	—	38 (67)	39 (68)	38 (67)	92 (12)	81 (41)	6 mo lumen diameter	Yes
Dake 2011/ 2013[25,26]	PTX-ES vs BMS	120	FII—FIV	125	—	—	—	—	—	—	—	—	—	—	—	—	—	Yes

ABI = ankle-brachial index; BMS = bare metal stent; BS = bare stent; CAD = coronary artery disease; DEB = drug-eluting balloon; DES = drug-eluting stent; EB = eluting balloon; EFS = event-free survival; ES = eluting stent; FII/FIII/FIV = Fontaine stage II, III, or IV; LLL = late lumen loss; MI = myocardial infarction; mo = month; *N* = number; PTA = balloon angioplasty; pts = patients; PTX = paclitaxel; RF = Rutherford; S = stent; SD = standard deviation; Sirol = sirolimus; TLR = target lesion revascularization; y = years.

[a] Data are based on the number of limbs, and not on the number of patients.

Summary of findings per comparison

Finally, the quality of evidence and the results of each trial were combined in one value to give an overview of the findings. When outcomes between strategies were significantly different ($p < .05$) in favor of the intervention strategy, the outcomes were scored as +, ++, or +++, depending on the corresponding quality of evidence. When a significant difference was in favor of the comparator strategy, the outcomes were scored as -, - -, or - - -, depending on the corresponding quality of evidence. When outcomes between strategies were not significantly different ($p \geq .05$) the outcomes were scored as =, = =, or = = =, depending on the corresponding quality of evidence. When conflicting evidence was present, and data could not be pooled, both qualities of evidence are depicted in the summary of findings table.

RESULTS

Study selection

The search yielded 3658 articles, 2758 in Medline and 900 in Embase. Removal of 427 duplicates resulted in 3231 articles to be assessed for eligibility based on title and abstract. This resulted in exclusion of 3167 articles. For 64 articles, full-text had to be assessed before deciding whether they were eligible for this systematic review. Thirty-four articles were excluded, as 21 were only abstracts for conference meetings, 12 were RCTs of below-the-knee intervention, and one was a protocol publication. Finally, 30 articles[5–34] were included in this review. Fig. 1 is a flow diagram of the selection process.

Study characteristics

Patients. The 30 included articles were publications of 23 clinical trials of 3314 patients in total. In these trials, 15 (20 publications,[5–24] 2156 patients) compared BS with PTA, one (2 publications,[25,26] 474 patients) DES with PTA, four (4 publications,[27–30] 320 patients) DEB with PTA, and four (6 publications,[25,26,31–34] 354 patients) DES with BS. Overall, for all studies reporting prevalence of IC and CLI, patients had IC in 85% and CLI in 15% of patients. For all trials, the mean age ranged between 64 and 73 years, patients were male in 66%, had diabetes in 37%, and were smokers in 58%. The mean lesion length per RCT ranged between 15 and 182 mm (median 68 mm). Full study characteristics of each RCT are shown in Table 1.

Comparisons. One trial[25,26] first randomized patients to DES or PTA, and when bailout stenting was indicated for the PTA group, patients were randomized to bailout DES or bailout stent. All DEB trials and the DES versus PTA trial used paclitaxel eluting balloons or stents, whereas for the DES versus BS trials heparin, sirolimus, or paclitaxel was used.

Outcomes. Follow-up of patients varied from 1 to 36 months. The primary end point reported for RCTs was 6-month or 1-year primary patency, binary restenosis, TLR, or late lumen loss. One trial[25,26] comparing DES with PTA, reported a semi-clinical outcome, that is 1-year event-free survival as a primary end point. No study had a clinical outcome as a primary end point.

Methodological quality and risk of bias

For most trials allocation concealment and sequence generation were performed adequately or were not sufficiently reported. One of the trials[19] had a high risk of bias for sequence generation, as randomization was based on patient identification number. No trial checked all risk factors for baseline differences, so therefore many were scored as unclear risk of bias for baseline characteristics. Nine trials[6–10,14,16,19,22,25,26,29] (39%) had differences in baseline characteristics, and were therefore subject to a high risk of bias. Blinding during intervention was not possible for trials comparing BS or DES with PTA, resulting into 20 (87%) studies[6–30] scored as a high risk of bias. For item blinding during outcome assessment, incomplete outcome data, and selective outcome reporting, the majority of trials were scored as adequate or unclear. Fourteen (61%) RCTs[5,9,10,14–18,20–22,24–27,31,33,34] scored high on 'other risk of bias', as more than 20% of patients dropped out for outcome assessment (11 RCTs), patients crossed over between arms (1 RCT), outcomes reported did not match between tables and text (1 RCT), or bailout stenting was not performed while over 30% stenosis remained present after PTA (1 RCT). Methodological quality per RCT is shown in Fig. 2, and overall methodological quality of RCTs per risk of bias item is shown in Fig. 3.

Summary of findings per comparison

The summary of findings for each comparison is depicted in Table 2. The outcomes extracted from every trial are shown Appendix 2 (online supplementary material). An overview of the quality of evidence per outcome is shown in Appendix 3 (online supplementary material). The summary findings per comparison are described below.

BS versus PTA. For most outcomes, results were available from several follow-up stages. For the outcomes walking capacity evaluated by questionnaire, Rutherford change, TLR, bypass, amputation, death, and MACE, the strategies of BS and PTA did not show significant differences at several time points.

For the outcomes treadmill walking capacity and binary restenosis, results were conflicting, showing overall an equal effect between BS and PTA, but also beneficial effect for both strategies at several follow-up stages. Fig. 4 shows a meta-analyses and forest plots of 12-month TLR, binary restenosis, and death.

DES versus PTA. Few data were available at different follow-up stages for all outcomes. For the outcomes TLR, patency, and EFS, low-quality evidence was available, showing a beneficial effect of a paclitaxel-DES over PTA. For the outcomes walking capacity evaluated by questionnaire, Rutherford improvement or change, amputation, and death, low-quality evidence was available, showing equal effect between both strategies.

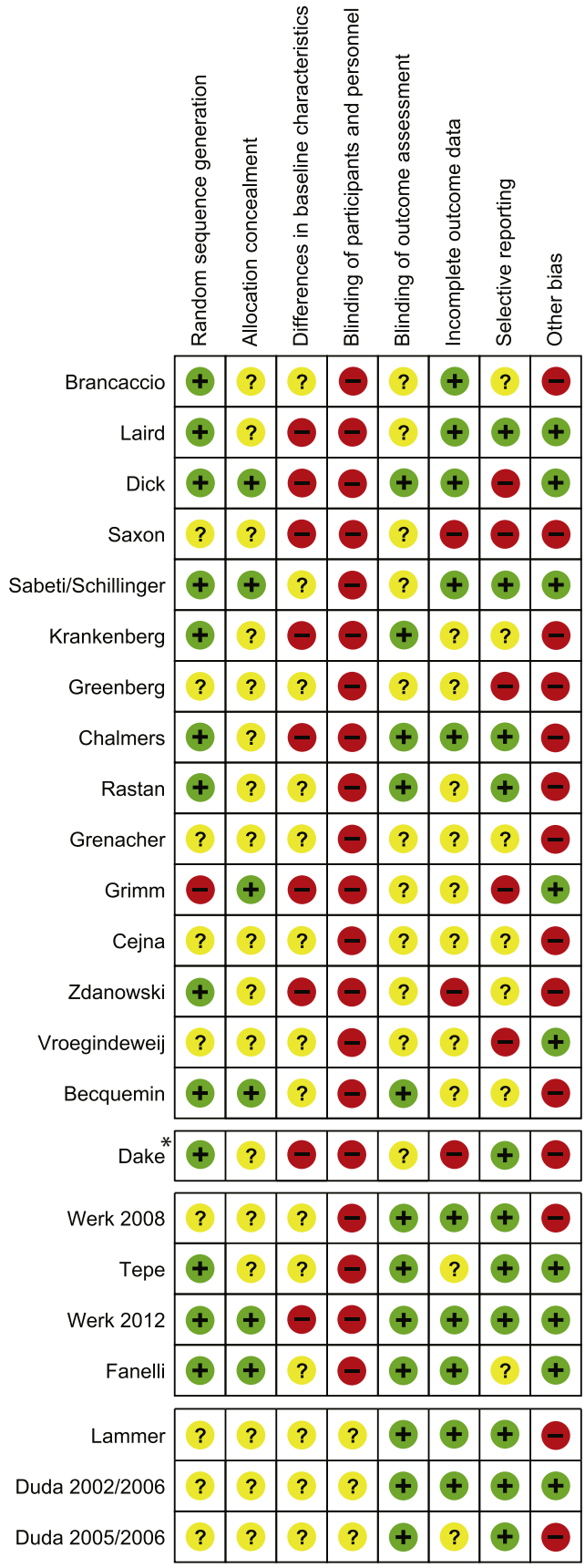

Figure 2. Methodological quality and risk of bias for each individual RCT. The items were scored as adequate (+), unclear (?), or inadequate (-). The figure is divided into four parts, from top to bottom, respectively, BS versus PTA, DES versus PTA, DEB versus PTA, and DES versus BS. * The studies of Dake et al. compared multiple strategies, that is DES versus PTA and DES versus BS.

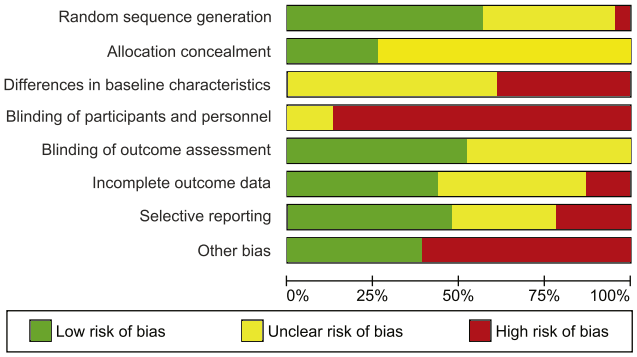

Figure 3. Methodological quality per item.

DEB versus PTA. For quality of life and walking capacity, no results were available. For other outcomes, results on multiple follow-up moments were available. Low- to moderate-quality of evidence showed a positive effect of paclitaxel-DEB compared with PTA for the outcome TLR, with a RR of 0.20 (95% CI: 0.10 to 0.42) at 6 months and 0.27 (95% CI: 0.16 to 0.47) at 24 months after meta-analysis. No differences between strategies were found for the outcomes Rutherford improvement or change, stenosis grade, amputation, and death at several follow-up stages. Fig. 5 shows a meta-analyses and forest plots of 6-month TLR and binary restenosis.

DES versus stent. Limited data were available at different follow-up time points for all outcomes, except for restenosis. For the outcomes reported on, DES performed equally compared to BS. For binary restenosis or patency most RCTs showed equal performance of strategies, and a minority of studies showed a lower restenosis rate after 12 months follow-up for the DES strategy.

DISCUSSION

Summary of evidence

The population evaluated had IC in 85% and CLI 15%. Overall, quality of evidence was low to moderate. The 15 trials comparing BS with PTA (with optional bailout stenting) showed, in general, that clinical outcomes did not differ between both interventions after 6 to 36 months follow-up. Only for treadmill walking capacity did BS show some beneficial effect over PTA. Little evidence is available comparing paclitaxel DES with PTA, and outcomes such as quality of life and walking capacity have not been studied. For ATK lesions, heparin-, sirolimus-, or paclitaxel-DES showed no consistent beneficial effect over the use of BS. The use of paclitaxel-DEB showed no significant differences compared with PTA for change in Rutherford classification. However, TLR rate was significantly lower until 24 months follow-up for the DEB strategy.

Table 2. Summary of findings per comparison.

BS vs PTA	1 mo	3 mo	6 mo	9 mo	12 mo	24 mo	36 mo
QoL questionnaire			= = =		= = =		= = =
Treadmill walking capacity			+++		+++/- -	= =	
Questionnaire walking capacity					= = =		= = =
RF change	= = =	= = =	= = =		= = =	= =	
TLR				= =	= = (MA)		= = =
Bypass					= = (MA)		
Binary restenosis		= = = (MA)	+++ (MA)/ = = =	= =	= = (MA)/ +++	++/= =/- - -	
Late lumen loss							
Stenosis grade							
Minor amputation	= = (MA)		= = =		= = = (MA)	= =	
Major amputation	= = (MA)		= = =		= = (MA)	= =	
Total amputation	= = (MA)		= = =	= =	= = = (MA)	= =	
Death	= = (MA)		= = = (MA)	= =	= = (MA)		= = =
MACE free			= = =	= =	= = =		
EFS							= = =

DES vs PTA	1 mo	3 mo	6 mo	9 mo	12 mo	24 mo	36 mo
QoL questionnaire							
Treadmill walking capacity							
Questionnaire walking capacity					=		
RF change						=	
TLR					++		
Bypass							
Binary restenosis						++	
Late lumen loss							
Stenosis grade							
Minor amputation					= =		
Major amputation					= =		
Total amputation					= =		
Death					= =	= =	
MACE free							
EFS					++	++	

DEB vs PTA	1 mo	3 mo	6 mo	9 mo	12 mo	18–24 mo	36 mo
QoL questionnaire							
Treadmill walking capacity							
Questionnaire walking capacity							
RF change			+/= =		= =	=	
TLR			+++ (MA)		+++	++ (MA)	
Bypass					++		
Binary restenosis			+++ (MA)			=	
Late lumen loss			+++ (MA)				
Stenosis grade			= =			=	
Minor amputation			= =		= =		
Major amputation			= = = (MA)		= =	=	
Total amputation			= =		= =		
Death			= = = (MA)		= =	=	
MACE free					++		
EFS							

DES vs BS	1 mo	3 mo	6 mo	9 mo	12 mo	24 mo	36 mo
QoL questionnaire							
Treadmill walking capacity							

Continued

Table 2-*continued*

DES vs BS	1 mo	3 mo	6 mo	9 mo	12 mo	24 mo	36 mo
Questionnaire walking capacity					=		
RF change					=		
TLR			=			=	
Bypass	= =		= =				
Binary restenosis			= =	=	++/= =	=	
Late lumen loss			= =				
Stenosis grade			= =				
Minor amputation	= =						
Major amputation	= =						
Total amputation	= =						
Death	= =		=			=	
MACE free							
EFS							

+, ++, or +++ refers to, respectively, very low-, low-, or moderate-quality evidence for a significant difference ($p < .05$) in favor of the intervention strategy. -, - -, or - - - refers to, respectively, very low-, low-, or moderate-quality evidence for a significant difference ($p < .05$) in favor of the comparator strategy (e.g. PTA). =, = =, or = = = refers to, respectively, very low-, low-, or moderate-quality evidence for non-significant difference ($p \geq .05$) between strategies. When conflicting evidence was present in trials, and data could not be pooled, both qualities of evidence were depicted.BS = bare stent; DEB = drug-eluting balloon; DES = drug-eluting stent; EFS = event-free survival; MA = meta-analysis; MACE = major adverse cardiac event; mo = month; PTA = balloon angioplasty; QoL = quality of life; RF = Rutherford; TLR = target lesion revascularization.

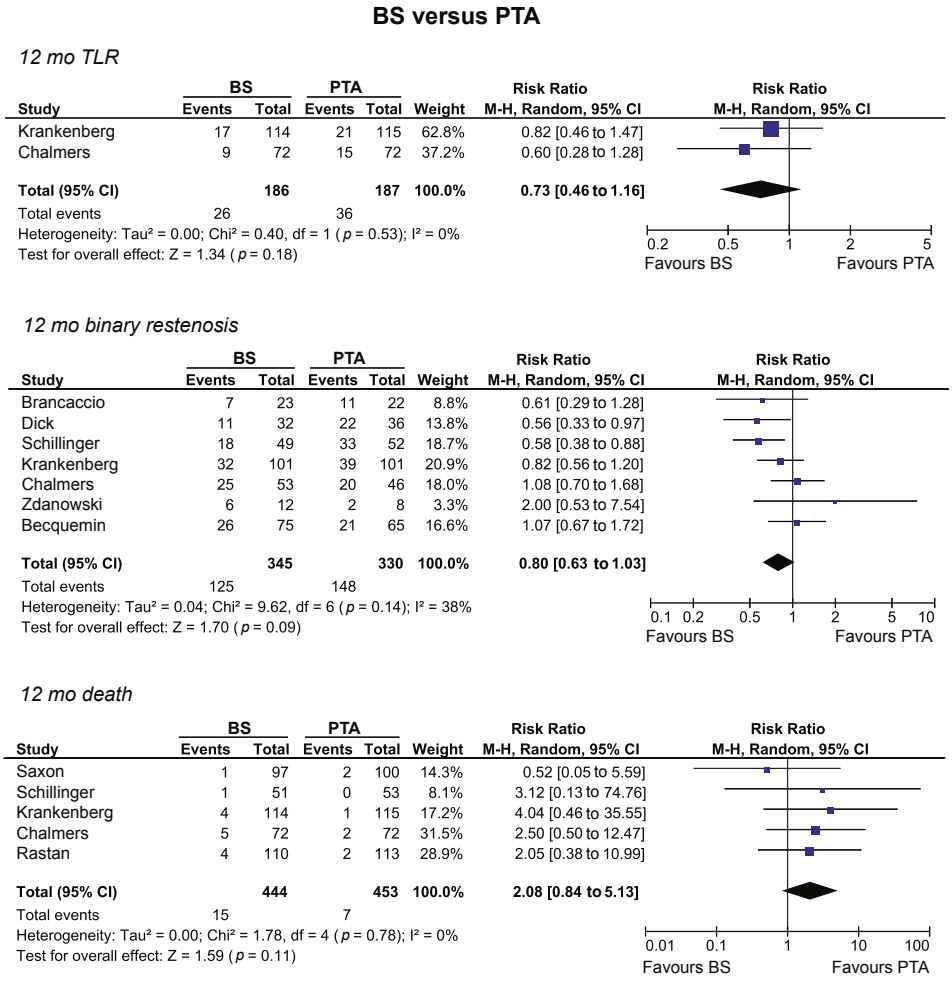

Figure 4. Forest plots of 12-month target lesion revascularization (TLR), binary restenosis, and death, of bare stent (BS) versus balloon angioplasty (PTA).

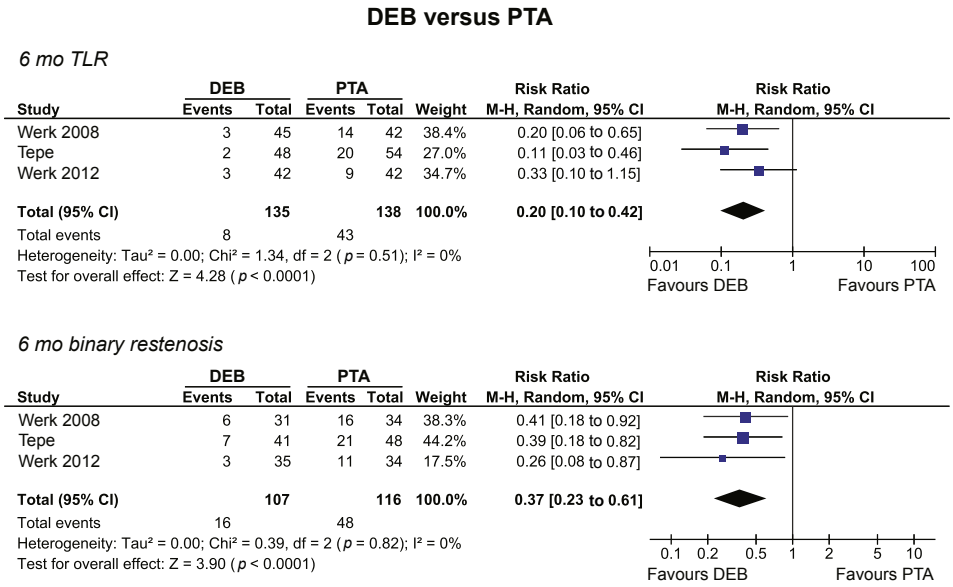

Figure 5. Forest plots of 6-month target lesion revascularization (TLR) and binary restenosis of drug-eluting balloon (DEB) balloon angioplasty (PTA).

Implications for practice

Endovascular revascularization strategies using primary BS, DES, or DEB do not evidently perform better than PTA with optional bailout stenting in terms of clinical outcomes. Therefore, endovascular treatment of ATK lesions in patients with IC should initially be performed using PTA, especially as PTA is much less expensive compared with the other treatment strategies.[15] When PTA does not result into less than 30% residual stenosis, or flow-limiting dissection occurs, bailout stenting may be performed. Stenting using DES is not preferred, as this review did not show a significant clinical benefit over the use of the less expensive BS. For patients with CLI, no substantial evidence with regard to clinical end points is available to recommend a specific endovascular treatment strategy in ATK lesions other than PTA with optional bailout stenting.

Limitations of this study

The recommendation given in this review is a general recommendation. As a result of the heterogenity between studies, a recommendation for a specific subgroup of patients cannot be given. For instance, studies differed in terms of lesion length, that is range of mean lesion length was 15 to 120 mm, the number of occlusions, and post-interventional antiplatelet protocols. Also the specific type of stents used differed between studies and patient population consisted of both IC and CLI patients in many trials. Therefore, for selected groups other strategies may be preferred, but should be studied first.

This systematic review encountered several flaws in the design of trials. First of all, data on the more important outcomes in the clinician's point of view for patients with IC, such as quality of life, walking capacity, and change in Rutherford classification, were reported in a minority of studies. Other clinical data such as amputation and death were reported in many studies, but these outcomes are only relevant for patients with CLI, being the minority of patients in most trials. Therefore, clinically relevant outcomes should be studied separately for patients with IC and CLI. Second, most trials were industry sponsored. In this review 13 trials were industry sponsored, five were investigator initiated, and five did not report whether they were sponsored. This may potentially result in bias, as a recent systematic review showed that industry sponsored studies more often have favorable efficacy results compared with studies that were sponsored by other sources.[36] Furthermore, many trials concerning new devices select a primary outcome which might show statistically significant differences more easily than clinical outcomes. Also clinical trials with clinical follow-up are more expensive, and therefore more difficult to get funded. Proof of clinical efficacy is in Europe not a prerequisite for CE mark registration, as is the case with new drugs. Therefore, most trials chose patency or late lumen loss as their primary end point, because such outcomes are easy to measure. Moreover, sample sizes were relatively small, as power calculations are based on these outcomes. As a result, studies were underpowered to be able to determine differences in clinically more relevant outcomes. To address this issue, we downgraded the quality of evidence when imprecision was present.

Third, several trials considered bailout stenting as a failure in patients allocated to PTA, and did not provide data with or without bailout stenting. We chose not to include these studies in our systematic review, as we consider bailout stenting to be part of the PTA strategy. As a result, potentially relevant data of these RCTs could not be used. Another issue considering bailout stenting was that the choice for placing a bailout stent was not always clearly defined or just not followed. For instance, in one study[16] it was stated that bailout stenting had to be performed when more than 30% residual stenosis remained after PTA.

However, although this was the case in 14 lesions, only four were treated with a bailout stent.

Future trials should include more homogeneous study populations, that is either patients with IC or CLI, and make a proper assessment as to the relevant clinical outcomes for the study population, for example wound healing for patients with CLI. Furthermore, power analyses should be based on the relevant clinical outcomes, bailout stenting should not be recorded as a failure, and a consistent antiplatelet protocol should be applied.

For interpreting the reliability of systematic reviews and meta-analysis, publication bias should be assessed, as it has been shown that only 63% of abstracts of RCTs presented at scientific meetings are published in full within 2 years.[37] Also, studies with 'positive' results are more frequently published than those without 'positive' results.[37] However, we could not study publication bias properly, as a single funnel plot could not be constructed because of the heterogeneity between studies in terms of outcome reporting and follow-up time. To address this shortcoming, the quality of evidence was downgraded one level for every outcome.

The results of this systematic review are only relevant for ATK arterial lesions. However, treating patients with IC or CLI should include the entire arterial tree, as a retrospective study showed that only 8% of the patients with IC or CLI had a single arterial lesion at the ATK level, whereas 92% also had one or multiple arterial lesions at the aortoiliac level or below the knee.[35]

CONCLUSION

In general, a low level of evidence suggests that performing PTA with optional bailout stenting for ATK lesions is the preferred endovascular strategy in patients with IC. For selected subgroups of IC, in terms of selected patient and lesion characteristics, optimal treatment strategies should be further studied. For patients with CLI more studies are needed, with a focus on quality of life, functional status, and limb salvage, for recommending the optimal treatment strategy. In future RCTs, clinical outcomes relevant to the patient population should be the primary end point.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY MATERIAL

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.ejvs.2014.02.011.

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